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Application: PCT/SI03/00024 (WO 2004/006933 A2)

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This is in response to the first written opinion according to Rule 66 PCT dated December 19, 2003

1. It is first of all requested to conduct a **detailed substantive examination**.

Further, applicant requests that a second written opinion is drawn up.

2. The Examiner mentions the documents WO 01/47933 (A), EP 0 733 634 (B), EP 0 733 635 (C) and US 5,229,382 (D) as relevant prior art documents.

3. The following are applicant's observations on these documents.

- 3.1. WO 01/47933 (A)

This document discloses new polymorphic forms of olanzapine, which are designated as form III, IV and V. The document also teaches methods for the preparation of these new polymorphic forms and pharmaceutical compositions containing them.

However, none of these polymorphic forms is identical to the polymorphic form (A) of olanzapine which is subject of the present invention.

Moreover, the document is silent about a process for the preparation of form I olanzapine, the specific solvates of olanzapine and a process for preparing anhydrous olanzapine by using such solvates, which all are subject matter of the present invention. Please compare claims 1, 6, 8, 10, 12, 14 and 16 of the present application.

3.2. EP 0 733 634 (B)

This document only describes the preparation of methanol, ethanol and 1-propanol solvates of olanzapine but does not disclose the polymorphic form A of olanzapine nor does it disclose the specific solvate forms of olanzapine, which are the subject matter of the present application

The document also discloses the use of the specific solvates of olanzapine for the preparation of only technical grade olanzapine.

In contrast to this, the process according to the present invention for the preparation of olanzapine and in particular of form I olanzapine results in a high yield of more than 95% which is clearly superior to the yield of 76.7% which is reported in example 1 of this document.

Moreover, the process according to the present invention allows the obtaining of olanzapine in a more pure form. In case of the present process the total chromatographic purity and assay of olanzapine were more than 99%, wherein the individual impurities were present below 0.1%, while on the other hand the purity of olanzapine as disclosed in this document, was only 98.1%.

3.3. EP 0 733 635 (C)

This document relates to crystalline form II of olanzapine which is said to be the more stable form. It is prepared by dissolving technical grade olanzapine in ethyl acetate and

crystallization from the resulting solution by any conventional process such as seeding, chilling, scratching the glass of the reaction vessel or other common techniques.

Neither polymorphic form A of olanzapine nor the solvates of olanzapine nor the processes for preparing olanzapine and form I olanzapine, which form subject matter at the present invention, are disclosed or suggested by this document.

3.4. US 5,229,382 (D)

This document describes olanzapine and a process for its preparation involving crystallization from acetonitrile. The product obtained was in EP 733 635 (C) referred to as form I olanzapine.

In contrast to this, the process according to claim 1 of the present application involves crystallization of olanzapine from a solvent mixture comprising 2-propanol. Thus, the present process is clearly novel with respect to this document.

Further, the process according to this document does not lead directly to pure olanzapine, but further extraction and chromatographic methods need to be used in order to obtain the required purity of the final product. The present process allows the preparation of form I olanzapine in very pure form even after completion of only the crystallization step from a solvent mixture comprising 2-propanol. Thus, the present process does not require the further purification methods as disclosed in the document.

Finally, the present process also provides a very high yield of olanzapine which can be higher than 95%.

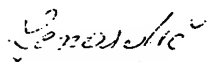
During our investigations in the field of the preparation of olanzapine, it has been shown that the yield of the process for preparing crude olanzapine as disclosed in Example 1 of this document is usually between 75% and 85%. Further on, the document reports that, after the crystallization step of crude olanzapine from acetonitrile, 1.65 g of pure olanzapine is obtained. When combined with the results of

our experiments, this gives us the yield of the crystallization step of the process of this document as in the range of only 38% to 43%. This is clearly inferior to the 95% yield for the process of the present invention.

In view of the above comments, it is clear that the subject matter of all claims is not only novel, but also involves an inventive step.

It is respectfully requested to reconsider and waive the objections in the light of the above submissions.

Industrial Property Department


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